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WADC TECHNICAL REPORT 55-198

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**CUTANEOUS TOXICITY EVALUATION
OF
FABRICS IMPREGNATED WITH ANTI-MILDEW AGENTS**

MORRIS V. SHELANSKI

CHARLES JOSEPHS

INDUSTRIAL TOXICOLOGY LABORATORY

MARCH 1955

WRIGHT AIR DEVELOPMENT CENTER

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AERO MEDICAL LABORATORY

CONTRACT No. AF 33(616)-2432

PROJECT No. 7159

WRIGHT AIR DEVELOPMENT CENTER
AIR RESEARCH AND DEVELOPMENT COMMAND
UNITED STATES AIR FORCE
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

FOREWORD

The research reported herein was performed by the staff of the Industrial Toxicology Laboratory, Inc., 3340 Chestnut Street, Philadelphia 4, Penna., under Air Force Contract No. AF 33(616)-2432, Project No. 54-670A-576, "Dermatological Research," with the Aero Medical Laboratory, Wright Air Development Center. This contract was in support of Project No. 7159, Task No. 71802, formerly initiated under RDO No. 698-31. Captain Edward F. Westlake, Jr. served as contract monitoring officer under the supervision of Dr. George Kitzes, Chief, Biochemistry Section.

The work was carried out and administered under the direction of the Philadelphia Air Procurement District, Middletown Air Material Area, 1411 Walnut Street, Philadelphia, Penna., with Mr. E. F. Barrett acting as Administrative Contracting Officer.

The following were actively engaged in the project: Dr. Morris V. Shelanski, Director of Industrial Toxicology Laboratory; Dr. Joseph V. Klauder, Consultant Dermatologist; Charles Josephs, Assistant to the Director; Louis Shelanski, Animal Physiologist; Karl Gabriel, Assistant.

ABSTRACT

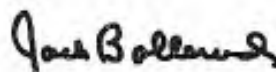
Fabrics impregnated with certain anti-mildew agents were studied via the prophetic patch test method on laboratory animals and volunteer human subjects to determine the primary irritant effect and the sensitization index of the impregnated cloth. The fabrics were impregnated with the following materials: 1,3-difluoro-4,6-dinitro benzene; 1-fluoro-3-chloro-4,6-dinitro benzene; 1-fluoro-3-bromo-4,6-dinitro benzene; 1-fluoro-3-methyl-4,6-dinitro benzene; 3,3'-difluoro-4,4'-dihydroxy biphenyl; 3,3'-5,5'-tetrafluoro-2,2'-dihydroxy biphenyl; 5-5'-difluoro-2,2'-dihydroxy biphenyl; Bis-(2-hydroxy-5-fluoro phenyl) sulfide. Other fabrics were studied which had been altered by the acetylation process or by the cyanoethylation process.

The patch test studies with laboratory animals indicated that all materials were non-irritating. On the human subjects this was not the case. Those fabrics which were impregnated with halogen substituted dinitrobenzenes elicited many strong reactions as evidence of primary irritation. They were not recommended for use on any material which would contact the human skin.

PUBLICATION REVIEW

This report has been reviewed and is approved.

FOR THE COMMANDER:



JACK BOLLERUD
Colonel, USAF (MC)
Chief, Aero Medical Laboratory
Directorate of Research

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INTRODUCTION

Industrial Toxicology Laboratory, Inc. was engaged by the United States Air Force to perform dermatological studies and provide cutaneous toxicity data on certain chemically impregnated fabrics. This data would serve as criteria for establishing safe handling procedures and limits of application of the impregnated fabrics. The chemical compounds, with which the fabrics had been impregnated, have been demonstrated to inhibit the growth of mildew.

There are various methods used for the determination of cutaneous toxicity of a chemical compound or substance. Laboratory animals, such as rabbits or guinea pigs, have been used by many investigators ^{1/}. The true index of cutaneous reaction can, however, only be determined by using human subjects. Prophetic patch tests are one of the methods used for this purpose ^{2/ 3/}. This test method helps to establish both the primary irritation and sensitization characteristics of a compound brought into contact with the human skin. Under the terms of Contract AF 33(616)-2432, prophetic patch test studies were performed on laboratory animals and volunteer human subjects, to establish the primary irritant and sensitization characteristics of certain specific chemically impregnated fabrics.

Submitted March 1955

MATERIALS

The following materials were received from the Aero Medical Laboratory, for study under terms of Contract No. AF 33(616)-2432.

1. Sample #2 -cloth impregnated with 1,3-difluoro-4,6-dinitro benzene. Approximately 0.68% by weight.
2. Sample #3 -cloth impregnated with 1-fluoro-3-chloro-4,6-dinitro benzene. Approximately 0.66% by weight.
3. Sample #4 -cloth impregnated with 1-fluoro-3-bromo-4,6-dinitro benzene. Approximately 0.61% by weight.
4. Sample #5 -cloth impregnated with 1-fluoro-3-methyl-4,6-dinitro benzene. Approximately 0.54% by weight.
5. Sample #9 -cloth impregnated with 3,3'-difluoro-4,4'-dihydroxy biphenyl. Approximately 1.7% by weight.
6. Sample #10 -cloth impregnated with 3,3'-5,5'-tetrafluoro-2,2'-dihydroxy biphenyl. Approximately 1.2% by weight.
7. Sample #11 - cloth impregnated with 5,5'-difluoro-2,2'-dihydroxy biphenyl. Approximately 0.94% by weight.
8. Sample #12 -cloth impregnated with Bis-(2-hydroxy-5-fluoro phenyl) sulfide. Approximately 1.4% by weight.
9. Control - Acetone Soaked Control Cloth for above samples.
10. Sample #1-13 -cotton fabric altered by acetylation process to contain 22.0% acetyl.
11. Sample #2-13 -cotton duck fabric, without softening agent, chemically altered by cyanoethylation process, nitrogen analysis 3.4-3.7%.
12. Control for Sample #2-13.

CRITERIA FOR GRADING PATCH TEST REACTIONS

Among the authors of textbooks and articles on cutaneous irritation and sensitization, there is little agreement on the criteria to be used for grading reactions which result from patch tests. The following are some examples of criteria used:

1. Some authors:

- 0 negative
- + slight erythema
- 1+ definite erythema
- 2+ marked erythema
- 3+ erythema plus vesicles
- 4+ erythema plus weeping vesicles

2. Criteria used by Schwartz:

- 0 no reaction - negative; questionable erythema too faint for one to call reaction positive
- 1+ clear cut erythema
- 2+ erythema plus edema or papules
- 3+ erythema plus edema plus vesiculation

3. Criteria used by Strauss:

- 1+ erythema
- 2+ erythema and edema
- 3+ erythema, edema, and vesiculation
- 4+ erythema, edema, vesiculation and oozing

4. Criteria used by Sulzberger and Bloch:

- 0 no reaction
- (+) mildest erythema
- + erythema
- ++ erythema and edema and/or beginning papulation or vesiculation
- +++ fully developed vesiculation, papulation, edema, bullae
- ++++ strongest reaction - denudation, necrosis, etc.

Intermediate reactions may be designated by combinations of these symbols. e. g., erythema and slight edema or a very few papules + to ++. Questionable reactions may be indicated by ?.

5. Criteria used by Industrial Toxicology Laboratory personnel during course of study:

- 1+ definite or clear cut erythema
- 2+ marked erythema, greater than present in 1+ reaction
- 3+ marked erythema, edema, with or without a few vesicles
- 4+ marked erythema, edema, with vesicles and oozing

RABBIT SCREENING STUDIES

PROCEDURE

Ten groups of five albino rabbits each were used in this study. The animals selected weighed approximately two kilograms each. Prior to use, the animals were placed on colony diet and observed for a period of two weeks. Animals not showing normal weight gain were replaced.

Prior to patching, the fur on the back of each rabbit was closely clipped to expose an area of skin equal to at least 10% of the total body area. This area was then shaved to completely denude the skin. The patch site area was marked with permanent ink to identify the site for later reference.

The chemically impregnated cloth (as supplied) was cut into pieces two inches square. The test material was applied to the denuded skin, covered with glassine paper, and held in place by means of a muslin binder. Five rabbits per material were used. The first or primary application remained in contact with the denuded skin for forty-eight hours. Upon removal, reactions were graded and recorded. Twenty-four hours after removal of the patches, the sites were examined for delayed reactions.

Following the primary application, the animals were rested for fourteen days. The patch material was then re-applied on the same site as a challenge or sensitization application. Again, after forty-eight hours contact, the patches were removed and reactions graded and recorded. Twenty-four hours later, the sites were examined for delayed reactions.

RESULTS

The results of the animal testing are shown in Table I. One rabbit showed a 1+ reaction to Sample No. 5 following removal of the primary application. There were no other reactions observed.

CONCLUSIONS

The patch test screening study on the denuded skin of albino rabbits indicated that none of the sample materials supplied under Contract AF 33 (616)-2432 were strong primary irritants or sensitizers on rabbits. The single 1+ reaction to Sample No. 5 was not significant and did not warrant classifying this sample a primary irritant.

HUMAN PATCH TESTS

The results of the animal screening study indicated that it was safe to continue the dermatological research using volunteer human subjects.

PROCEDURE

Groups of normal, healthy, male volunteer subjects, aged 18-35 were used in this study. Each material was tested on a total of at least 300 subjects, except where indicated.

The chemically impregnated fabric (as supplied) was cut into patches one inch square. The test patches were applied to the volar surface of the forearms, covered with lintine discs 1 1/4 inches in diameter, protected by glassine paper and held in place with half inch adhesive tape. Three materials were applied to the right arm, two materials plus one control were applied to the left arm. Two applications were made in accordance with the Schwartz Patch Test Method. The first application, to determine primary irritation and the second or challenge application, to determine possible sensitization. The primary application remained in contact with the skin for forty-eight hours. Upon removal all reactions were graded and recorded. Twenty-four hours later, the sites were examined for delayed reactions.

Following removal of the primary application, the subjects were rested for two weeks. The second or challenge application was then applied. This patch also remained in contact with the cutaneous surface of the forearm for forty-eight hours. Upon removal, reactions were graded and recorded. Twenty-four hours later, the sites were examined for delayed reactions.

RESULTS

The results of the human patch test studies are shown in Table II. During the course of the study, it was necessary to discontinue studies with materials No. 2 (cloth impregnated with 1,3-difluoro-4,6-dinitro benzene), No. 3 (cloth impregnated with 1-fluoro-3-chloro-4,6-dinitro benzene), No. 4 (cloth impregnated with

1-fluoro-3-bromo-4, 6-dinitro benzene), and No. 5 (cloth impregnated with 1-fluoro-3-methyl-4, 6-dinitro benzene) due to strong primary irritation elicited by these materials. None of the other materials under study evidenced any reactions indicative of primary irritation or sensitization.

CONCLUSIONS

Sample No. 2 - cloth impregnated with 1, 3-difluoro-4, 6-dinitro benzene. Approximately 0.68% by weight.

Proved to be a strong primary irritant. Twenty-three subjects exposed to this sample for twelve hours showed four 1+ reactions, six 2+ reactions and three 3+ reactions. Number reacting to patch - 56%.

Thirty-four subjects exposed to sample for one hour showed four 1+ reactions and two 2+ reactions. Number reacting to patch - 17%.

Fabric impregnated with this compound, at the concentration indicated, should not be brought into contact with the human skin. Contact for a period of only a few minutes will elicit some cutaneous irritation.

Sample No. 3 - cloth impregnated with 1-fluoro-3-chloro-4, 6-dinitro benzene. Approximately 0.66% by weight.

Proved to be very strong primary irritant. Twenty-three subjects exposed to this sample for twelve hours showed two 1+ reactions, eleven 2+ reactions and six 3+ reactions. Number reacting to patch - 82%.

Thirty-four subjects exposed to sample for one hour showed eight 1+ reactions, nineteen 2+ reactions and two 3+ reactions. Number reacting to patch - 85%.

Fabric impregnated with this compound, at the concentration indicated, should not be brought into contact with the human skin. Contact for a period of only a few minutes will elicit cutaneous irritation.

Sample No. 4 - cloth impregnated with 1-fluoro-3-bromo-4, 6-dinitro benzene. Approximately 0.61% by weight.

Proved to be very strong primary irritant. Twenty-three subjects exposed to this sample for twelve hours showed three 1+ reactions, five 2+ reactions and seven 3+ reactions. Number reacting to patch - 65%.

Thirty-four subjects exposed to sample for one hour showed ten 1+ reactions, twelve 2+ reactions and three 3+ reactions. Number reacting to patch - 73%.

Fabric impregnated with this compound, at the concentration indicated, should not be brought into contact with the human skin. Contact for a period of more than a few minutes will elicit cutaneous irritation.

Sample No. 5 - cloth impregnated with 1-fluoro-3-methyl-4, 6-dinitro benzene Approximately 0.54% by weight.

Proved to be a very strong primary irritant. Twenty-three subjects exposed to this sample for twelve hours showed three 1+ reactions, eight 2+ reactions, and six 3+ reactions. Number reacting to patch - 73%.

Thirty-four subjects exposed to this sample for one hour showed twelve 1+ reactions and six 2+ reactions. Number reacting to patch - 52%.

Fabric impregnated with above compound, in the concentration indicated, should not be brought into contact with human skin. Exposure to the material for only a few minutes may elicit some cutaneous reactions.

Sample No. 9 - cloth impregnated with 3, 3'-difluoro-4, 4'-dihydroxy biphenyl. Approximately 1.7% by weight.

Sample No. 10 - cloth impregnated with 3, 3'-5, 5'-tetrafluoro-2, 2'-dihydroxy biphenyl. Approximately 1.2% by weight.

Sample No. 11 - cloth impregnated with 5, 5'-difluoro-2, 2'-dihydroxy biphenyl. Approximately 0.94% by weight.

Sample No. 12 - cloth impregnated with Bis-(2-hydroxy-5-fluoro phenyl) sulfide. Approximately 1.4% by weight.

Sample No. 1-13 - cotton fabric altered by acetylation process to contain 22.0% acetyl.

Sample No. 2-13 - cotton duck fabric, without softening agent, chemically altered by cyanoethylation process, nitrogen analysis 3.4-3.7%.

The above samples were patch tested on a total of three hundred subjects. There were no immediate or delayed reactions noted upon removal of the primary and the challenge applications.

Fabrics impregnated with or altered by the above chemical compounds, in the concentration indicated, are neither primary irritants nor sensitizers. Contact with the skin should not evidence any cutaneous reactions.

DISCUSSION

Prior to patch testing new chemical compounds on human subjects, screening studies are usually performed using laboratory animals. These screening studies help to eliminate compounds or materials which are strong primary irritants or sensitizers. However, it is possible that certain materials will be non-reactive on animal skin and yet elicit strong irritation on human skin. This was evident with samples #2, 3, and 4. These impregnated cloths produced no cutaneous reactions when patched on rabbits. The same materials on human patch test subjects elicited reactions of 1+, 2+ and 3+ intensity within one hour. After twelve hours of exposure to these materials, more than 50% of the subjects showed some skin reactions to the patch applications. This lack of correlation between results obtained with laboratory animals and those obtained with human subjects clearly illustrates that a comprehensive screening study must encompass patch testing on laboratory animals and on small groups of human subjects. Materials passing the screening phase can then be patched on large groups of human subjects.

Under the terms of Contract AF 33 (616)-2432, the method for patch testing the impregnated samples is well defined. This method is in accordance with the Schwartz technique ^{2/} and is generally used for determination of primary irritation and sensitization. On occasion, materials which have been demonstrated to be neither primary irritants nor sensitizers by this method have elicited cutaneous reactions after being in repeated and prolonged contact with the skin. Soaps, detergents and cosmetics are typical of formulations which will cause such a reaction. Repeated exposure of the skin to such materials will gradually produce evidence of cutaneous irritation. This has been termed a "fatigue" reaction ^{3/}. Many materials in repeated and prolonged contact with the human skin are capable of "fatiguing" the repair mechanism of the skin and can elicit reactions which are neither a result of primary irritation nor sensitization.

Our studies show that cloth samples #9, 10, 11 and 12, impregnated with anti-mildew agents, are neither primary irritants nor sensitizers by the Schwartz method of patch testing. Some of these samples, in repeated and prolonged contact with the skin, might produce a fatigue reaction. Using the present method of testing, such a reaction would not become evident until hundreds or even thousands of impregnated garments had been issued and worn. To preclude such an occurrence, this laboratory suggests the Repeated Insult Patch Test as a more realistic method for patch testing materials which will be in prolonged contact with the skin.

The repeated insult patch test differs somewhat from other patch test methods. The procedure is as follows: the test sample is applied to the skin of the subjects for twenty-four hours and then is removed. Skin reactions are graded and recorded. The skin is then allowed to recuperate for twenty-four hours. This cycle of contact and recuperation is repeated fifteen times for a total of thirty days, the reactions being graded after each application. Following the removal of the fifteenth application, the skin is allowed to recuperate for two to three weeks. The material is then re-applied on the same subjects for twenty-four hours. At the end of this period, the patches are removed and reactions are graded and recorded. The first application gives an index of primary irritation. The final application gives information on sensitization. The repeated applications, from the second to the fifteenth, determine the extent of fatiguing. Since this test method accelerates skin reactions, it is possible to forecast probability of cutaneous irritation due to long term exposure. The information supplied by the Repeated Insult Patch Test method could speed acceptance and reduce the cost necessitated by the introduction of new chemical compounds.

SUMMARY

1. All materials submitted under this contract were patch tested on both laboratory animals and volunteer human subjects for cutaneous primary irritation and sensitization reactions in accordance with the Schwartz Patch Test method.
2. Due to evidence of strong primary irritation, four of the twelve materials submitted were discontinued after being patched on fifty-seven human subjects.
3. Limits of exposure for each material is contained in the body of this report.
4. Suggestions for patch testing of materials which are in repeated or prolonged contact with the skin are included in this report.

TABLE I
RESULTS OF PATCH TESTS ON RABBITS

Sample Material #2 1, 3-difluoro-4, 6-dinitro benzene	*P	**C
Rabbit # 1	0	0
2	0	0
3	0 Two	0
4	0 Week	0
5	0 Interval	0
	0	0
Sample Material #3 1-fluoro-3-chloro-4, 6-dinitro benzene		
Rabbit # 1	0	0
2	0	0
3	0 Two	0
4	0 Week	0
5	0 Interval	0
	0	0
Sample Material #4 1-fluoro-3-bromo-4, 6-dinitro benzene		
Rabbit # 1	0	0
2	0	0
3	0 Two	0
4	0 Week	0
5	0 Interval	0
	0	0
Sample Material #5 1-fluoro-3-methyl-4, 6-dinitro benzene		
Rabbit # 1	0	0
2	0	0
3	0 Two	0
4	0 Week	0
5	1+ Interval	0
	0	0
Sample Material #9 3, 3'-difluoro-4, 4'-dihydroxy biphenyl		
Rabbit # 1	0	0
2	0	0
3	0 Two	0
4	0 Week	0
5	0 Interval	0
	0	0

Table I (continued)

	*P	**C
Sample Material #10		
3, 3'-5, 5'-tetrafluoro-2, 2'-dihydroxy biphenyl		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
	Two	
	Week	
	Interval	
Sample Material #11		
5, 5'-difluoro-2, 2'-dihydroxy biphenyl		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
	Two	
	Week	
	Interval	
Sample Material #12		
Bis-(2-hydroxy-5-fluoro phenyl) sulfide		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
	Two	
	Week	
	Interval	
Control for Samples #2, 3, 4, 5, 9, 10, 11, 12		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
	Two	
	Week	
	Interval	
Sample Material #1-13		
Cotton fabric altered by acetylation process		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
	Two	
	Week	
	Interval	

Table I (continued)

	*P	**C
Sample Material #2-12		
Cotton duck fabric chemically altered by cyanoethylation process		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
Control for Sample #2-13		
Rabbit # 1	0	0
2	0	0
3	0	0
4	0	0
5	0	0

- * Primary application - 48 hours duration
 ** Challenge application - 48 hours duration

TABLE II - A
RESULTS OF PATCH TESTING ON HUMAN SUBJECTS

Primary Patch

Material	No. Subjects	Hours Patched	<u>Primary Patch</u> Reaction after Removal				
			0	1+	2+	3+	4+
#2-cloth impregnated with 1, 3-difluoro-4, 6-dinitro benzene.	34	1	28	4	2	0	0
	23	12	10	4	6	3	0
#3-cloth impregnated with 1-fluoro-3-chloro-4, 6-dinitro benzene.	34	1	5	8	19	2	0
	23	12	4	2	11	6	0
#4-cloth impregnated with 1-fluoro-3-bromo-4, 6-dinitro benzene.	34	1	9	10	12	3	0
	23	12	6	3	5	7	0
#5-cloth impregnated with 1-fluoro-3-methyl-4, 6-dinitro benzene.	34	1	16	12	6	0	0
	23	12	6	3	8	6	0
#9-cloth impregnated with 3, 3'-difluoro-4, 4'-dihydroxy biphenyl.	300	48	300	0	0	0	0
#10-cloth impregnated with 3, 3'-5, 5'-tetrafluoro-2, 2'- dihydroxy biphenyl.	300	48	300	0	0	0	0

TABLE II - A
(continued)

Material	No. Subjects	Hours Patched	Primary Patch Reactions after Removal				
			0	1+	2+	3+	4+
#11-cloth impregnated with 5, 5'-difluoro-2, 2'-dihydroxy biphenyl.	300	48	300	0	0	0	0
#12-cloth impregnated with Bis-(2-hydroxy-5-fluoro phenyl) sulfide.	300	48	300	0	0	0	0
Control - acetone soaked control cloth for above samples.	300	48	300	0	0	0	0
#1-13-cotton fabric altered by acetylation process to contain 22.0% acetyl.	300	48	300	0	0	0	0
#2-13-cotton duck fabric, without softening agent, chemically altered by cyanoethylation process, nitrogen analysis, 3.4-3.7%.	300	48	300	0	0	0	0
Control for #2-13	300	48	300	0	0	0	0

TABLE II - B

RESULTS OF PATCH TESTING ON HUMAN SUBJECTSChallenge Patch

Material	No. Subjects	Hours Patched	<u>Challenge Patch</u> Reaction after Removal				
			0	1+	2+	3+	4+
#2-cloth impregnated with 1, 3-difluoro-4, 6-dinitro benzene.	0		Not Applied				
#3-cloth impregnated with 1-fluoro-3-chloro-4, 6-dinitro benzene.	0		Not Applied				
#4-cloth impregnated with 1-fluoro-3-bromo-4, 6-dinitro benzene.	0		Not Applied				
#5-cloth impregnated with 1-fluoro-3-methyl-4, 6-dinitro benzene.	0		Not Applied				
#9-cloth impregnated with 3, 3'-difluoro-4, 4'-dihydroxy biphenyl.	300	48	300	0	0	0	0
#10-cloth impregnated with 3, 3'-5, 5'-tetrafluoro-2, 2'- dihydroxy biphenyl.	300	48	300	0	0	0	0
#11-cloth impregnated with 5, 5'-difluoro-2, 2'-dihydroxy biphenyl.	300	48	300	0	0	0	0

TABLE II - B
(continued)

Material	No. Subjects	Hours Patched	Challenge Patch Reaction after Removal				
			0	1+	2+	3+	4+
#12-cloth impregnated with Bis-(2-hydroxy-5-fluoro phenyl) sulfide.	300	48	300	0	0	0	0
Control-acetone soaked control cloth for above samples.	300	48	300	0	0	0	0
#1-13-cotton fabric altered by acetylation process to contain 22.0% acetyl.	300	48	300	0	0	0	0
#2-13-cotton duck fabric, without softening agent, chemically altered by cyanoethylation process, nitrogen analysis 3.4- 3.7%.	300	48	300	0	0	0	0
Control for #2-13	300	48	300	0	0	0	0

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